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|---|---|
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/642,277 | Applicant(s) FINKLESTEIN ET AL. | |
|---|---|---|---|
| | Examiner Sita Pappu | Art Unit 1636 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants response to the Notice to comply with sequence rules, filed 04/22/2002, in paper # 15 has been entered. Letter to the draftsperson with the formal drawings, filed 02/05/2002, in paper # 10 and in paper # 16, filed 04/22/2002 is acknowledged. Claims 1-48 are pending in the instant application. This paper contains an examination of the claims 1-48.

### *Drawings*

Formal Drawings mailed in paper #16 (04/22/2002) were reviewed by the draftsperson and approved.

Formal drawings filed in paper #10 (01/16/2002) were previously reviewed by the draftsperson and the draftsperson objected to the formal drawings filed in paper #10. The type is peeling off because of the irradiation treatment the incoming mail is subjected to. Please see attached PTO-948 (02/12/2002) that corresponds to the Formal Drawings of Paper #10 (01/16/2002).

### *Priority*

Applicant's claim of priority to the provisional application 60/149,561 filed 08/18/1999 is acknowledged.

### *Claim Objections*

Claims 13, 14, 38, 39, 42, 43, 48 are objected to because of the following informalities: Claims 13, 14, 38, 39, 42, 43, 48 recite SEQ ID Nos with periods in between as follows: "SEQ.ID.Nos". Appropriate correction by removing the periods is required.

***In the specification***

The disclosure is objected to because of the following informalities:

Brief description of Figures on pages 5 and 6 refers to both Figure 1 and Figures 1A through 1D; and to both Figure 2 and Figures 2A through 2D. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transplanting neural stem cells together with FGF as the neural stimulant wherein the method results in increased integration and differentiation of neural stem cells and ameliorates the effects of ischemic injury in a rat model, does not reasonably provide enablement for a method of treating a subject with CNS damage and a kit or a pharmaceutical composition comprising stem cells and a neural stimulant for the treatment of brain damage. Further, the specification is not enabling for the use of the method of the invention in treating the various diseases claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 1-48 are directed to a method of treating a subject with CNS damage, said method comprising administering to said patient: cells and a neural stimulant wherein the conjoint administration of cells and neural stimulant ameliorates the effects of CNS damage and to a kit or pharmaceutical composition comprising stem cells and a neural stimulant for the treatment of brain damage. Therefore, the nature of the invention is directed toward cell transplantation therapy using neural stem cells or hematopoietic stem cells together with polypeptide growth factors or other neural stimulants and administering them to treat a subject who experienced ischemic stroke in the brain and to treat a variety of diseases such as Alzheimers', Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis, multiple sclerosis.

Breadth of the Claims:

The claims encompass a method of treating a subject with CNS damage (claims 1-35) using the kit of claims 36-43 or pharmaceutical composition of claims 44-48, said method comprising administering to said patient: cells and a neural stimulant wherein

the conjoint administration of cells and neural stimulant ameliorates the effects of CNS damage, wherein the CNS damage is a result of stroke, trauma, hypoxia, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis or Parkinson's disease, and thereby cover all organisms including human beings and encompass a method of treating all the claimed diseases in all the claimed organisms. Further, the claims encompass administration of any cells. Thus, the claims encompass cell transplantation therapy, to treat a variety of diseases in a variety of subjects or organisms using the method of the instant invention and, therefore, have a very broad scope.

Amount of Direction provided and existence of working examples:

The prior art teaches a method of administering neural stem cells or basic fibroblast growth factor to ameliorate ischemic injury in rats. However, prior art does not teach a method of administering neural stem cells and/or basic fibroblast growth factor alone or together for the purpose of cell transplantation therapy in subjects, in particular humans, to such levels that a therapeutic effect is obtained. In cases where prior art does not teach how to use the method, all the guidance for practicing the invention must come from the specification. The specification discloses a method of administering neural stem cells or basic fibroblast growth factor to ameliorate ischemic injury in rats but fails to disclose how long the enhanced recovery in rats lasts, and whether it is long enough to see a therapeutic effect. The working examples do not provide sufficient guidance on how to determine the appropriate dosage, and other parameters such as the best route of administration, and frequency of administration.

Examples provided in the specification (page 41) describe that administration of neural stem cells and basic fibroblast growth factor enhances stroke recovery in a model of stroke recovery in rats that underwent focal cerebral infarction surgery. Example 1 discloses the recovery experienced by rats that underwent focal cerebral infarction surgery by electrocoagulation of the middle cerebral artery, where the neural stem cells and the bFGF were both administered intracisternally, either alone or together. The specification on page 42, line 33, discloses that all three treatments, NSC, bFGF and the combination significantly enhanced recovery compared to placebo. The specification, further discloses on page 43, line 2, that no differences among treatments compared to placebo were seen on the body swing test, and that the trend toward superior enhancement of function seen in the combination group compared to the NSC and bFGF groups alone was nonsignificant (page 43, line 3-4). Image analysis for infarct volume (page 43, line 7) disclosed that no significant differences were seen among the groups although there was a trend toward a smaller infarct volume in the NSC group. Other than this, the specification, in this example, does not disclose any other therapeutically useful information such as how long the said effect lasted and whether it is sufficient to have a therapeutic effect. Further, this example does not provide sufficient guidance on how this method can be extrapolated to in vivo use in other subjects, in particular, human. The specification does not provide sufficient guidance in this example on the dosage, frequency of administration required and the best mode of administration, because this example disclosed that a single dose of conjoint administration of NSC and bFGF, administered intracisternally did not have a

significant therapeutic effect compared to NSC and bFGF alone, either in the phenotypic tests or in the infarction volume in the rat model of stroke recovery.

Example 2 discloses the recovery experienced by rats that underwent focal cerebral infarction surgery by electrocoagulation of the proximal middle cerebral artery (page 44, line 4), where the neural stem cells were administered intracerebrally and the bFGF was administered intracisternally, either alone or together (page 44, line 9), and that there was a trend towards best recovery in the combination group (page 45, line 5). Histological evaluation of the brains was still pending at the time the application was filed (page 45, line 6). The specification discloses that (page 45, line 12) example 2 "supports the notion that the combination of stem cell and growth factor treatment is superior to either treatment alone in enhancing stroke recovery" and that both examples were done (page 45, lines 14-16) using only one dose of NSC and growth factor and that further studies are underway to define the dose response characteristics of the interaction. Other than this, the example 2 does not demonstrate for how long this effect was observed and the level of combination treatment needed to achieve a therapeutic result compared to the administration of NSC and bFGF alone and whether repeat applications were necessary and if so, how frequently they were needed and, specifically, as disclosed in the specification, there is insufficient guidance on the dosage requirements, such that one of skill in the art would accept that their method would result in a therapeutic outcome and be able to practice the method using the guidance provided in the specification. In particular when application of this method of treatment to humans is considered, the only guidance provided in the specification is

the dosage scaling disclosed in Table 2 on page 34 where the doses determined in rats are scaled up for human treatments (page 33, line 14) based on body weight or brain surface area or by brain weight. It is unpredictable how much dose would be needed for human patients based on this guidance provided, especially when the specification on the same page (page 33, line 10) discloses that "administration of cells and other treatments may be carried out by various methods, and the method need not be the same for each component" and that that the molecule can be administered by any route of administration, and that "the dose may vary depending on the method of administration". It would be difficult to predict the brain weight of a human being such that an appropriate dose can be administered, and further, when "dosage may vary depending on the method of administration", it would require undue experimentation on the part of a skilled artisan to determine an appropriate method of administration and the dosage and scale it appropriately to the body weight and/or brain weight of a subject. It is well known in the clinical field that dosages that are not appropriately calculated based on the correct body weight for each patient are frequently ineffective.

Therefore, it is not predictable that the results obtained in rats correlate to results expected in humans such that one of skill would have reasonable expectation of obtaining therapeutic levels of treatment using the method of the instant invention. It is unpredictable how long the enhanced recovery due to the combination treatment would last such that a therapeutic effect is seen using the method of the instant invention. It would require undue experimentation on the part of a skilled artisan to determine the

dosage, frequency and route of administration, to obtain a level of treatment that would result in a therapeutic effect.

State of the art:

At the time of filing, *in vivo* cell transplantation therapy utilizing the neural stem cells was considered to be in its infancy. Park et al. (1999, Journal of Neurotrauma, vol. 16, pp 675-687) state that many questions still need to be answered (page 677, left column, paragraph 3) and that they " are still trying to learn how best to isolate these cells and characterize them" (page 677, left column, bottom paragraph, line 4). Further, Park et al. state that "to understand how best to unlock the capabilities of the NSC" (page 677, right column, line 9) one cannot be therapeutically driven in one's pursuits, but rather biologically motivated. This clearly establishes the state of the cell transplantation therapy field, at the time of filing, as one that needs further biological investigations before one can attempt to apply the neural stem cell science to the treatment of any disease.

Kmiec (1999; American Scientist, vol. 87, pp240-247), states that in the field of gene therapy, "limited success in animal models all too often leads directly to clinical trials (page 245, middle column, paragraph 2), which is also applicable to the field of cell transplantation therapy considering that the field is perceived to be still in its infancy, as stated above by Park et al. (1999). Thus, animal models in this field are not truly reflective of success in humans and are thus, unpredictable. Thus, it would require undue experimentation on the part of a skilled artisan to use the instant invention in any host.

Further, Barker and Rosser (2001, Drug Discovery Today, vol. 6, no. 11, pp 575-582) state that "the major problem confronting the field is in persuading neural precursor cells to differentiate into the phenotype required", which is "dopaminergic neurons in the case of parkinson's disease" and that "no replacement approaches using cells or viral vectors have entered the clinical arena for the treatment of" Parkinson's or Huntington's diseases" (page 580, right column, paragraph 2). Thus, even though the field of cell transplantation therapy using neural stem cells is considered very promising, the progress in understanding the biology of the neural stem cells has not approached a point where therapeutic uses of these cells in treating diseases is considered predictable.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the art to achieve cell transplantation at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of neural cell integration and differentiation, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of integration and differentiation in an art recognized animal model or patient as claimed.

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the

working examples do not provide sufficient guidance to practice the invention as claimed. The specification describes preliminary attempts at the use of the method in only rats and does not predict success in humans. Therefore, in the absence of specific guidance and working examples, the use of the claimed method of treating a subject with CNS damage comprising administering cells and neural stimulant is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Further, the method of the instant invention uses a rat model of stroke recovery wherein the rat experiences ischemic injury to the brain which is not an appropriate model for all the diseases covered by the claims. For example, Parkinson's disease is a neurodegenerative disorder of CNS (Barker and Rosser, 2001, page 575, right column, line 11) with distinct pathobiology and clinical features that are different from the rat model of the instant invention. Similarly, Huntington's disease is an inherited neurological disease comprising progressive motor, cognitive and psychiatric problems (Barker and Rosser, 2001, page 575, right column, bottom paragraph). It is unpredictable that the rat ischemic model of the instant invention would serve as an appropriate model for all the claimed diseases such that a skilled artisan would be able to use the information provided for the rat model to treat all the diseases covered by the claims.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of neural cell integration and differentiation following administration of neural and/or hematopoietic stem cells or other cell types together with a neural stimulant, the lack of guidance provided by the specification for the parameters affecting delivery, dosage, frequency, level of integration and differentiation, the lack of guidance concerning the treatment of various diseases using the claimed method of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed method for the purpose of treating a subject for the variety of claimed diseases as disclosed in the specification. Thus the specification does not enable one skilled in the art to use the claimed invention in a method of treating a subject with CNS damage.

Claims 13, 27, 38, 42, 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkor, 19UGPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" Vas-Cath Inc. v. Mahurkar 19UGPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath

Inc. v. Mahurkar 19UGPQ2d at 1116.

While the specification provides adequate written description for the claimed invention (methods and products) only with regard to the SeqID NO:1, 2 and 3, the specification fails to describe the other species within the genus of "polypeptides at least 30% identical to a bFGF polypeptide of SEQ ID NO:1, 2 or 3". The specification fails to describe a representative number of the sequences encompassed by the said genus by their complete structure and other identifying characteristics, with particularity to indicate that applicants had possession of the claimed invention. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying charecteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc. 45 USpQ2d 1641, 1646 (1995). In the instant case, the claimed methods of using sequences other than those of SEQ ID NO:1, 2 or 3 encoding a bFGF polypeptide, lack a written description. The specification fails to describe what other sequences fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed sequences isolated from any and all species, particularly polypeptide sequences that have the requisite biologiocal activity. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating

it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Lfd, 18 USPQ2d 1016 (Fed. Cir. 1991).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. However, in the instant case, three specific polypeptide sequence species of human bFGF polypeptide (SEQ ID NO:1, 2 or 3) are described. However the claims encompass all sequences at least 30% identical to SEQ ID NO:1, 2 or 3. Thus, the specification must describe a representative number of the encompassed species by their complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, since structure and/or function cannot be predicted from sequence, no identifying characteristics are provided for the claimed genus of sequences. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of all the sequences that are encompassed by the claims, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed sequences.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 15, 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite in its recitation of "polypeptide show in one of". Replacing the term "show" with "shown" is suggested.

Claims 15, 29 are indefinite in their recitation of "selected from the following group:", which is improper Markush language. Use of claim language such as "selected from the group consisting of" is suggested.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Rosen et al. (1999; WO200071715A1).

Although the kit is not enabled for its intended use, the component of the kit itself is disclosed in the prior art.

The kit of claims 41-43 comprises a device for obtaining a stem cell sample from a subject and a neural stimulant wherein the neural stimulant is a polypeptide of SEQ ID Nos. 1-3 or a polypeptide that is 30% identical to SEQ ID Nos. 1-3. The claimed kit reads on a device and a neural stimulant only, and not on the presence of a stem cell

sample in the kit. The presence of a device in the kit does not result in a structural difference between the claimed neural stimulant and the prior art.

Rosen et al. (1999) disclose the sequence of human fibroblast growth factor 11(pages 241-242) that is 99.7% identical to SEQ ID NO:1 and 100% identical to SEQ ID NO:2 of the instant invention.

The applicant claims an article of manufacture comprising a device and a neural stimulant. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art."

The intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, there are no claimed distinguishing features between the claimed kit and that of Rosen et al. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition in the kit is disclosed in the prior art.

Claims 36-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Flax et al. (1998; Nature Biotechnology vol. 16, pp.1033-1039).

Claims 36-43 are drawn to a kit for treatment of brain damage comprising stem cells and a neural stimulant, the kit further comprising apparatus for administering said stem cells and apparatus for administering said neural stimulant.

Although the kit is not enabled for its intended use, the kit itself is disclosed in the prior art.

The applicant claims an article of manufacture comprising stem cells, and/or a neural stimulant wherein the neural stimulant is a polypeptide growth factor. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Flax et al. (1998) teach the neural stem cells and fibroblast growth factor in culture (page 1037, right column, bottom paragraph, lines 2-9).

The feature of the neural stem cells expressing a vmyc gene is an inherent property of undifferentiated neural stem cells as disclosed by Flax et al. (1998). See page 1034, left column, paragraph 3.

Further, the apparatus for administering the stem cells and/or the growth factor does not patentably distinguish the claimed invention of claims 36-39 and 41-43 from the prior art because a variety of apparatii for administering the stem cells and/or the polypeptide growth factor is/are known in the art and can be used and the apparatus

used does not result in a structural difference between the prior art and the claimed invention of stem cells and polypeptide growth factor.

Thus, by teaching all of the limitations of claims 36-39, 41-43, Flax et al. clearly anticipated the instant invention.

Claims 44-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Carpenter et al (1997).

Although the pharmaceutical composition is not enabled for its intended use, the composition itself is disclosed in the prior art.

Carpenter et al. (1997) disclose a human CNS neural stem cell culture with fibroblast growth factor (column 3, line 47 and the table following it).

The presence of a pharmaceutically acceptable carrier in the composition does not result in a structural difference between the claimed composition and the prior art.

Since the claim is directed to a composition, the intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, as there are no claimed distinguishing features between the

claimed pharmaceutical composition and that of Carpenter et al., the pharmaceutical property is an inherent feature of the product. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition is disclosed in the prior art.

Claims 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Caput et al. (1990; FR 2642086A).

Although the kit is not enabled for its intended use, the component of the kit itself is disclosed in the prior art.

The kit of claims 41-43 comprises a device for obtaining a stem cell sample from a subject and a neural stimulant wherein the neural stimulant is a polypeptide of SEQ ID Nos. 1-3 or a polypeptide that is 30% identical to SEQ ID Nos. 1-3.

Caput et al. (1990) disclose the sequence of basic fibroblast growth factor (see Fig. 8 of FR2642086A) that is identical to SEQ ID NO:1 and to SEQ ID NO:2 (see figure 3 of FR2642086A) of the instant invention.

The claimed kit reads on a device and a neural stimulant only, and not on the presence of stem cell sample in the kit. The presence of a device in the kit does not result in a structural difference between the claimed neural stimulant and the prior art.

The applicant claims an article of manufacture comprising a device and a neural stimulant. The MPEP states that,".. in apparatus, article, and composition claims,

intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art."

The intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, there are no claimed distinguishing features between the claimed kit and that of Caput et al. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition in the kit is disclosed in the prior art.

Claims 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Moscatelli et al. (1987; EP226181A).

Although the kit is not enabled for its intended use, the component of the kit itself is disclosed in the prior art.

The kit of claims 41-42 comprises a device for obtaining a stem cell sample from a subject and a neural stimulant wherein the neural stimulant is a polypeptide that is 30% identical to SEQ ID Nos. 1-3. The claimed kit reads on a device and a neural

stimulant only, and not on the presence of a stem cell sample in the kit. The presence of a device in the kit does not result in a structural difference between the claimed neural stimulant and the prior art.

Moscatelli et al. (1999) disclose the sequence of human angiogenic factor protein from placental tissue (claim 7, page 49) that is 67% identical to SEQ ID NO:1 and 54% identical to SEQ ID NO:2 of the instant invention.

The applicant claims an article of manufacture comprising a device and a neural stimulant. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art."

The intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, there are no claimed distinguishing features between the claimed kit and that of Rosen et al. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition in the kit is disclosed in the prior art.

Claims 41-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Senoo et al. (1989; EP326907A).

Although the kit is not enabled for its intended use, the component of the kit itself is disclosed in the prior art.

The kit of claims 41-43 comprises a device for obtaining a stem cell sample from a subject and a neural stimulant wherein the neural stimulant is a polypeptide of SEQ ID Nos. 1-3 or a polypeptide that is at least 30% identical to SEQ ID Nos. 1-3. The claimed kit reads on a device and a neural stimulant only, and not on the presence of a stem cell sample in the kit. The presence of a device in the kit does not result in a structural difference between the claimed neural stimulant and the prior art.

Senoo et al. (1989) disclose the sequence of basic fibroblast growth factor (claim 8, page 22, Fig.8) that is 100% identical to SEQ ID NO:3 of the instant invention.

The applicant claims an article of manufacture comprising a device and a neural stimulant. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art."

The intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. See MPEP 2111.02. In

the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, there are no claimed distinguishing features between the claimed kit and that of Rosen et al. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition in the kit is disclosed in the prior art.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Although the method of the invention is not enabled for therapeutic use in any subject to treat a variety of diseases, the method itself would have been obvious at the time of the invention.

Claims 1-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andsberg et al. (1998; European Journal of Neuroscience vol. 10. no.6, pp.2026-2036), Alp et al. (U.S. Patent S No. 5,733,871) further in view of Ip et al. (1994; PCT International Publication Number WO 94/03199) and Daughaday et al. (1989, Endocr. Rev. 10:68-91).

Andsberg et al. (1998 ) teach the use of neural stem cells in a rat stroke model.

Andsberg et al. (1998) do not teach the use of a neural stimulant such as a fibroblast growth factor.

US patent 5,733,871 (03/31/1998) is directed to the use of bFGF in a method for preventing or limiting cell death due to ischemia, hypoxia or neurodegeneration (see claim 1). Further Daughaday et al. (1989, Endocr. Rev. 10:68-91) teach that IGF-1 and IGF-2 promote recovery from various insults to CNS.

Ip et al. (1994) teach that treating neuronal precursor cells with a member of the FGF family and a member of the CTNF family enhances their effectiveness and survival

(see abstract and page 13, line 24) and demonstrated the promise of combination approach in increasing the effectiveness of neural stem cells.

Therefore, it would have been obvious to one of ordinary skill in the art to be motivated to use the combination approach of using the stem cells and the bFGF together in a method for preventing cell death or stimulating the growth of new neurons, with a reasonable expectation of success. The motivation to do so and the expectation of success was provided by the teachings of Ip et al. (1994) who successfully demonstrated the synergistic effect of using a combination approach in increasing the effectiveness of the neural stem cells.

Thus, the method of the instant invention would have been prima facie obvious to one of skill in the art at the time of the invention.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 872 9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson, at (703) 305-2982.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
June 14, 2002